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Diastolic Function in Hypertrophic Cardiomyopathy: Relation to Exercise Capacity

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Doppler echocardiography was used to assess diastolic function in 40 patients with hypertrophic cardiomyopathy and to relate it to the patients' symptoms, anaerobic threshold and maximal oxygen consumption during cardiopulmonary exercise testing. The patients had a smaller early (E wave) ($p < 0.01$), higher late (A wave) ($p < 0.05$) mitral diastolic flow velocity, larger A/E ratio ($p < 0.01$), longer isovolumetric relaxation time and E wave duration ($p < 0.001$) and slower deceleration rate of the E wave ($p < 0.001$) than 40 age- and gender-matched normal subjects. In the patients with hypertrophic cardiomyopathy, maximal oxygen consumption and anaerobic threshold were, respectively, 26.3 ± 9.2 and 21.1 ± 6.1 ml/kg per min compared with 47 (range 39 to 68) ($p < 0.01$) and 41 (range 27 to 58) ml/kg per min ($p < 0.01$) in normal subjects. There was no relation between Doppler indexes and symptoms but symptomatic patients had lower maximal oxygen consumption and anaerobic threshold compared with asymptomatic patients (21.4 ± 7 vs. 30.7 ± 10, $p < 0.001$ and 18.6 ± 4.7 vs. 23.1 ± 5.7, respectively, $p < 0.001$).

In conclusion, Doppler echocardiography can identify abnormalities of left ventricular filling in patients with hypertrophic cardiomyopathy. However, these indexes measured at rest do not correspond to the patient's professed symptomatic status or exercise capacity measured objectively. Conversely, cardiopulmonary exercise testing reveals a depressed maximal oxygen consumption and anaerobic threshold even in the least symptomatic patients.

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Hypertrophic cardiomyopathy is a primary disorder of heart muscle that is characterized by left ventricular hypertrophy without identifiable cause. Whereas systolic function is seldom depressed, diastolic dysfunction is a prominent feature of this disorder (1–5). The introduction of Doppler echocardiography has provided a noninvasive means of assessing ventricular diastolic function (6–15) and has been shown to correlate well with indexes of left ventricular function obtained by gated radionuclide ventriculography (11) and cardiac catheterization (14).

Previous studies (12) have documented abnormalities of diastolic function using pulsed wave Doppler ultrasound in patients with hypertrophic cardiomyopathy under rest conditions. These studies have noted a wide range of patterns including normal velocity curves and a poor correlation between symptoms and appearance of the mitral valve flow velocity curves (12). In this study we investigated the range of filling abnormalities in patients with hypertrophic cardiomyopathy using pulsed wave Doppler ultrasound and related these findings to the patients' exercise functional capacity and symptomatic status.

Methods

Study patients (Tables 1 and 2). Forty patients with hypertrophic cardiomyopathy were studied. The clinical diagnosis of hypertrophic cardiomyopathy was confirmed by the echocardiographic demonstration of a hypertrophied left ventricle with normal or decreased internal dimensions in the absence of any cardiac or systemic cause of hypertrophy (1–5). There were 22 female and 18 male patients with an average age of 41 years (range 13 to 74). Seventeen patients were entirely asymptomatic and 13 were mildly symptomatic (short of breath) in New York Heart Association functional class I or II, whereas 3 were in functional class III or IV. Three patients gave a history of one or more syncopal attacks and 2 had presyncopal episodes with ventricular tachycardia; 19 had exertional chest pain (Table 1). All patients remained on medication during evaluation, including a beta-adrenergic blocking agent in 14, amiodarone in 38 and verapamil in 4. The pattern of hypertrophy was asymmetric in 33 patients (83%), concentric in 5 (12%) and distal in 2 (5%) (Table 2).

An additional 40 age- and gender-matched normal volunteers selected from doctors and personnel working in our

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Table 1. Clinical Characteristics of 40 Patients With Hypertrophic Cardiomyopathy

Age (mean) (yr)	41 (range 13–74)
Male/female	22/18
NYHA class	
I–II	13 (33%)
III–IV	3 (8%)
Syncope/presyncope	5 (13%)
Chest pain	19 (48%)
Asymptomatic	17 (43%)

NYHA class = New York Heart Association classification.

institution, without clinical or echocardiographic evidence of cardiovascular disease, were similarly studied to constitute the control group. All patients and control subjects were in sinus rhythm.

Doppler echocardiography. Each subject underwent a complete echocardiographic study (16) followed by color flow imaging and pulsed and continuous wave Doppler ultrasound, using Toshiba SSH 65A and 160A ultrasound systems. Simultaneous electrocardiographic (ECG) and phonocardiographic recordings were also obtained. From apical transducer positions the sample volume was placed in the left ventricular inflow at the center of the mitral funnel during unforced expiration. Care was taken to obtain the highest early and late peak left ventricular diastolic inflow velocity with the best signal to noise ratio. Values were averaged from five successive beats in each subject.

The following Doppler echocardiographic indexes were obtained for each subject: 1) maximal early and late diastolic flow velocity (E and A waves), as well as the A/E ratio; 2) isovolumetric relaxation time measured as the time between the aortic closure sound (A_2) and the onset of mitral diastolic flow (ms); 3) duration of early diastolic flow velocity (ms); and 4) mean deceleration rate of early diastolic flow velocity (EF slope) (cm/s^2).

Color flow imaging of the intraventricular flow profile was used to ascertain the presence of intraventricular turbulence (17) and mitral regurgitation (18), followed by continuous wave Doppler recordings of the maximal left ventricular outflow tract flow velocity.

Table 2. Echocardiographic and Doppler Ultrasound Characteristics of 40 Patients With Hypertrophic Cardiomyopathy

	No.	%
Distribution of hypertrophy		
Asymmetric	33	83
Concentric	5	12
Distal	2	5
Systolic anterior motion		
Yes	27	68
No	13	32
Mitral regurgitation		
Mild	16	40
Moderate	4	10
Severe	—	—
Intraventricular systolic flow velocity (m/s)		
High (3.7 ± 1.4)	20	50
Low (1.2 ± 0.3)	20	50

Exercise test. All patients underwent progressive treadmill exercise testing using a modified Bruce protocol with simultaneous respiratory gas analysis according to a previously described technique (19,20). The test was performed within 3 to 5 days of the echocardiographic examination without altering the patients' medication or loading conditions. Patients were encouraged to exercise until they felt unable to continue. Sampling of mixed expired gases was performed every second and data were expressed as 10-s mean values. Maximal oxygen consumption was defined as the mean of the highest two oxygen consumption values obtained during exercise. Anaerobic threshold was defined as the point at which carbon dioxide production increased disproportionately in relation to oxygen consumption obtained from a graph plotting oxygen consumption against carbon dioxide production. Values for oxygen consumption and carbon dioxide production were expressed in ml × kg-1 × min-1 (20).

Twenty (50%) of the 40 normal subjects also underwent exercise testing with respiratory gas analysis to establish the normal range of maximal oxygen consumption and anaerobic threshold; these results have been published elsewhere (20). Maximal oxygen consumption and anaerobic threshold were 39 to 68 (mean 47) and 27 to 58 (mean 41) ml/kg per min in these normal subjects.

Statistical analysis. Data were expressed as mean values ± 1 SD. Comparison between patients and normal subjects and between groups of patients was performed by using the unpaired *t* test for paired data. Statistical relations were evaluated by correlation coefficient and linear regression analysis.

Results

Echocardiographic findings. A left ventricular outflow tract gradient was detected in 20 (50%) of the 40 patients. The average left ventricular outflow tract flow velocity was 3.7 ± 1.4 m/s (range 2 to 6.4) in these 20 patients; in the remaining 20 patients it was 1.2 ± 0.3 m/s (0.8 to 1.5), $p < 0.001$.

Mitral regurgitation was also present in 20 (50%) of the 40 patients, 18 of whom also had a left ventricular outflow tract gradient. Two patients with a left ventricular outflow tract gradient had no mitral regurgitation, whereas two others with mild mitral regurgitation did not have a gradient. The mitral regurgitation was considered mild in 16 patients and moderate in 4.

Diastolic flow characteristics (Table 3). Patients with hypertrophic cardiomyopathy differed significantly as a group from normal subjects in each of the Doppler indexes of diastolic function. They exhibited lower early diastolic flow velocity ($p < 0.001$), higher late diastolic flow velocity ($p < 0.05$), higher A/E ratio ($p < 0.01$), longer isovolumetric

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Table 3. Doppler Indexes in 40 Normal Subjects and 40 Patients With Hypertrophic Cardiomyopathy

	E Wave (cm/s)	A Wave (cm/s)	A/E	IVRT (ms)	EF (cm/s^2)	DF (ms)
Normal	61.7 ± 12.6	38.7 ± 9.1	0.65 ± 0.21	64.7 ± 13	463 ± 125	220 ± 38
HCM	51.4 ± 11.9	45.8 ± 19.4	0.93 ± 0.44	94.8 ± 27.9	233 ± 101	304 ± 71
p value	<0.001	<0.05	<0.01	<0.001	<0.001	<0.001

A wave = late diastolic filling; A/E = ratio between late and early left ventricular diastolic filling; DF = duration of early diastolic filling; E wave = early diastolic filling; EF = deceleration rate of early diastolic filling; HCM = hypertrophic cardiomyopathy; IVRT = isovolumetric relaxation time.

relaxation time ($p < 0.001$), slower deceleration of the early diastolic flow velocity ($p < 0.001$) and prolongation of the early diastolic flow velocity ($p < 0.001$).

Relation between symptoms and diastolic flow at rest (Table 4). Nineteen (83%) of 23 symptomatic patients and 11 (65%) of 17 patients without symptoms had at least one Doppler diastolic index outside the 95% confidence limits derived from the normal subjects. The remaining four (17%) symptomatic and six (35%) asymptomatic patients had normal diastolic indexes, but this difference did not reach statistical significance.

Cardiopulmonary exercise test. This test was terminated by breathlessness or fatigue, or both, in all patients. Maximal oxygen consumption and anaerobic threshold were 26.3 ± 9.2 and 21.1 ± 6.1 ml/kg per min, respectively. In all but two patients (95%) these values were lower than those observed in the normal control group ($p < 0.001$). Those two patients, aged 17 and 23 years, respectively, were younger members of families with hypertrophic cardiomyopathy; they were asymptomatic and had been diagnosed during routine screening of their respective families.

Correlation between exercise capacity and symptoms (Table 4). Seventeen asymptomatic patients (42%) had impaired maximal oxygen consumption and anaerobic threshold when compared with the normal subjects ($p < 0.01$). Twenty-three patients (58%) were symptomatic; 16 complained of shortness of breath, 19 had chest pain and 5 had at least one episode of syncope or presyncope. As a group, symptomatic patients had a lower maximal oxygen consumption (21.4 ± 7 vs. 30.7 ± 10, $p < 0.002$) and lower anaerobic threshold (18.6 ± 4.7 vs. 23.1 ± 5.7, $p < 0.01$) than did asymptomatic patients, but exercise capacity was best related to breathlessness. Patients with more pronounced functional disability (functional class III or IV) had worse exercise performance, whereas asymptomatic patients and those with mild breathlessness (functional class I or II) had better exercise performance ($p < 0.05$). Exercise capacity was not related to the presence or absence of an intraventricular gradient.

Correlation between exercise capacity and Doppler diastolic indexes. There was a weak negative correlation between the A/E ratio and both maximal oxygen consumption ($r = -0.381$, $p < 0.02$) and anaerobic threshold ($r = -0.422$, $p < 0.02$), primarily because of a positive correlation between the E wave and maximal oxygen consumption ($r = 0.415$, $p < 0.01$) and anaerobic threshold ($r = 0.355$, $p < 0.02$). The A wave was inversely related to the maximal oxygen consumption ($r = -0.258$, $p = 0.086$) and anaerobic threshold ($r = -0.350$, $p < 0.05$). Of the 10 patients with normal Doppler diastolic indexes, 9 had depressed maximal oxygen consumption and anaerobic threshold; 6 of these patients were asymptomatic under rest conditions.

Relation between gradients and diastolic flow characteristics (Table 5). Twenty patients (50%) had a left ventricular outflow tract gradient. Their early diastolic flow velocity (E wave) did not differ from that of patients without a gradient. The late diastolic flow velocity (A wave), however, was generally higher in patients with an outflow tract gradient ($p < 0.05$), but the A/E ratio was similar in the two groups.

Discussion

Shortness of breath, chest pain and dizziness or syncope are the most frequent symptoms leading to the discovery of patients with hypertrophic cardiomyopathy. Although it is commonly believed that dyspnea is related to increased left atrial pressure caused by the stiff left ventricle and its high diastolic pressure (5), recent studies (20) have demonstrated that the ability to increase cardiac output is the major determinant of exercise capacity. In this study we failed to identify a relation between Doppler diastolic variables, necessarily measured under rest conditions, and the symptomatic status of patients. In these patients the abnormal

Table 4. Relation Between Symptoms, Doppler Diastolic Indexes and Gas Exchange During Exercise in 40 Patients With Hypertrophic Cardiomyopathy

	No.	E Wave (cm/s)	A Wave (cm/s)	A/E	IVRT (ms)	EF (cm/s^2)	DF (ms)	VO_2 max (ml/kg per min)	Anaerobic Threshold (ml/kg per min)
Symptomatic	23	51.5 ± 12.8	45.5 ± 22	0.95 ± 0.5	95 ± 26	237.5 ± 110	312 ± 72	21.4 ± 7*	18.6 ± 4.7*
Asymptomatic	17	51.3 ± 11	46.3 ± 16	0.92 ± 0.6	93 ± 30	227 ± 92	227 ± 92	30.7 ± 10*	23.1 ± 5.7*

*$p < 0.001$. VO_2 max = maximal oxygen consumption; other abbreviations as in Table 3.

Table 5. Comparison of Patients With and Without an Intracavitary Gradient

	E Wave	A Wave	A/E	IVRT	EF	DF
Gradient	52.6 ± 13.9	52.7 ± 22.4	1.05 ± 0.5	89.2 ± 26.9	219 ± 107	313 ± 83
No gradient	50.2 ± 9.6	38.6 ± 13.7	0.8 ± 0.3	100.4 ± 28.5	244.5 ± 97.7	293.8 ± 59
p value	NS	<0.05	NS	NS	NS	NS

Abbreviations as in Table 3.

response to cardiopulmonary exercise testing confirmed the functional abnormality and was related to symptomatic status.

Doppler diastolic indexes. Often in patients with hypertrophic cardiomyopathy, the period during which the heart is isovolumetric is prolonged, filling is slow and the proportion of filling volume resulting from atrial systole may be increased (21). These pathophysiologic changes are reflected in the pulsed Doppler recording of the mitral inflow waveform (10,12,14). Impaired ventricular relaxation usually results in slowed early ventricular filling and a compensatory exaggerated atrial systolic filling in patients with normal left atrial pressure (14). In more severe cases, however, with increased left atrial pressure, the mitral inflow velocity may be normalized (14). With more advanced disease, with decreased compliance, there is accelerated rapid early filling and normal or reduced late filling and a restrictive pattern (14). In this study, one or more abnormal indexes of left ventricular filling determined by pulsed wave Doppler ultrasound were detected in 75% of patients with hypertrophic cardiomyopathy. This finding is in accordance with previous reports (10,12) demonstrating lower early and higher late diastolic flow velocities, prolongation of isovolumetric relaxation time and slower deceleration of the early diastolic flow velocity in these patients than in normal persons. Conversely, 10 (25%) of our patients with hypertrophic cardiomyopathy had, similar to the normal subjects, entirely normal Doppler diastolic indexes. Of these 10 patients, 4 were very symptomatic—3 with breathlessness and 1 with angina—indicating that the normal indexes may have represented a period of pseudonormalization in the progression from the prolonged relaxation with increased late filling ("early phase") to the phase of restriction with reduced late filling seen in advanced disease (14,21). It is therefore not surprising that Doppler diastolic indexes are not specific for a particular symptomatic status and exercise capacity of patients with hypertrophic cardiomyopathy and provide little diagnostic information in cross-sectional studies.

Maximal oxygen consumption and anaerobic threshold. Exercise testing associated with respiratory gas analysis provides an objective assessment of exercise capacity that can be monitored serially. Maximal oxygen ventilatory capacity (VO_2 max) can be moderately reduced even in asymptomatic patients (20). In our study, although normal and abnormal Doppler diastolic indexes occurred similarly in symptomatic and asymptomatic patients at rest, 95% of all patients had an abnormal response to cardiopulmonary exercise. Exercise performance was not related to the presence of an intracavitary gradient.

The majority (77%) of patients with a poor response to cardiopulmonary exercise testing also had impaired Doppler diastolic indexes at rest, even though 26% of this subgroup were asymptomatic. This finding suggests that subclinical diastolic dysfunction shown by abnormal diastolic indexes at rest may precedes the development of symptoms.

Conclusions. In this study we confirmed that patients with hypertrophic cardiomyopathy often exhibit filling abnormalities on pulsed wave Doppler echocardiography but these are not always related to the patient's professed symptomatic status. Cardiopulmonary exercise testing may reveal a depressed maximal oxygen consumption and anaerobic threshold even in the least symptomatic patients.

Asymptomatic patients with hypertrophic cardiomyopathy who had normal Doppler diastolic indexes at rest performed better on cardiopulmonary exercise testing (as assessed by maximal oxygen consumption and anaerobic threshold) than did patients with abnormal indexes. Symptomatic patients with abnormal rest Doppler diastolic indexes had a lower anaerobic threshold during cardiopulmonary exercise. More severely affected patients with depressed systolic function and no outflow tract gradient had normal diastolic indexes, indicating that a period of pseudonormalization may precede the development of a restrictive pattern. Further sequential studies are needed to identify progression of abnormalities and the prognostic implications in these patients.

References

1. Wigle ED, Heimbecker RO, Gunton RW. Idiopathic ventricular septal hypertrophy causing muscular subaortic stenosis. Circulation 1962;26:325–40.
2. Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis: a description of the disease based upon an analysis of 64 patients. Circulation 1964;30(suppl IV):IV-3–119.
3. Goodwin JF, Oakley CM. The cardiomyopathies. Br Heart J 1972;34:545–52.
4. Epstein SE, Henry WL, Clark CE, et al. Asymmetric septal hypertrophy. Ann Intern Med 1974;81:650–80.
5. Oakley CM. The cardiomyopathies. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. Oxford Textbook of Medicine. Vol II, 2nd ed. Oxford: Oxford Medical Publishers, 1987;13:209–29.
6. Fujii J, Yazaki Y, Sawada H, Aizawa T, Watanabe H, Kato K. Noninvasive assessment of left and right ventricular filling in myocardial infarction with a two-dimensional Doppler echocardiographic method. J Am Coll Cardiol 1985;5:1155–60.

7. Channer KS, Culling W, Wilde P, Jones JV. Estimation of left ventricular end-diastolic pressure by pulsed Doppler ultrasound. Lancet 1986;1: 1005–7.
8. Rokey R, Kuo LC, Zoghbi WA, Limacher MC, Quinones MA. Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography: comparison with cineangiography. Circulation 1985;71:543–50.
9. Spirito P, Maron BJ, Bonow RO. Noninvasive assessment of diastolic function: comparative analysis of Doppler echocardiographic and radionuclide techniques. J Am Coll Cardiol 1986;7:1263–71.
10. Takenaka K, Dabestani A, Gardin JM, et al. Left ventricular filling in hypertrophic cardiomyopathy: a pulsed Doppler echocardiographic study. J Am Coll Cardiol 1986;7:1263–71.
11. Kitabatake A, Inoue M, Asao M, et al. Transmitral blood flow reflecting diastolic behavior of left ventricle in health and disease: a study by pulsed Doppler technique. Jpn Circ J 1982;46:92–102.
12. Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 1987;10:733–42.
13. Appleton CP, Hatle LK, Popp RL. Demonstration of restrictive ventricular physiology by Doppler echocardiography. J Am Coll Cardiol 1988; 11:757–68.
14. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular function: new insights from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol 1988:12:426–40.
15. St. Goar FG, Gibbons R, Schnittger I, Valantine HA, Popp RL. Doppler echocardiographic changes soon after cardiac transplantation. Circulation 1990:82:872–8.
16. Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two dimensional real time ultrasound imaging of the heart and great vessels: technique, image orientation, structure identification and validation. Mayo Clin Proc 1978; 53:271–303.
17. Yock PG, Hatle L, Popp RL. Patterns and timing of Doppler-detected intracavitary and aortic flow in hypertrophic cardiomyopathy. J Am Coll Cardiol 1986;8:1047–58.
18. Kinoshita N, Nimura Y, Okamato M, Miyatake K, Nagata S, Sakakibara H. Mitral regurgitation in hypertrophic cardiomyopathy: non-invasive study by two dimensional Doppler echocardiography. Br Heart J 1983; 49:574–83.
19. Davies NJ, Dennison DM. The measurement of metabolic gas exchange and minute volume by mass spectrometry alone. Resp Physiol 1979;36: 261–7.
20. Frenneaux MP, Porter A, Caforio AL, Odawara H, Counihan PJ, McKenna WJ. Determinants of exercise capacity in hypertrophic cardiomyopathy. J Am Coll Cardiol 1989;13:1521–6.
21. Wigle ED. Hypertrophic cardiomyopathy: a 1987 viewpoint. Circulation 1987;75:311–22.